39. (New) In a method for preparing a detergent composition, which includes the step of combining a detergent composition with, as an active ingredient, at least one mutated high alkaline protease, the improvement which comprises no detectable wild-type high alkaline protease with said mutated high alkaline protease.

40. (New) In a method for processing laundry, which includes the step of contacting said laundry with a detergent composition which has as an active ingredient at least one mutated high alkaline protease, the improvement which comprises no detectable wild-type high alkaline protease with said mutated high alkaline protease.--.

## REMARKS

The Claimed Invention

The claimed invention is directed to methods and compositions for preparation of mutant high alkaline proteases and non-reverting endogenous extracellular protease-negative alkalophilic and/or asporogenic Bacillus strains which produce the mutant high alkaline protease in the absence of the endogenous extracellular protease. The present invention is further directed to a detergent composition comprising as an active ingredient at least one mutant high alkaline proteases produced according to the method of the invention and a laundry process employing the detergent composition.

The Pending Claims

Prior to entry of the above amendments, claims 4-7, 9-15, 19, and 23-37 are pending. Claims 23, 4-7, 9-11, 26 and 28 are directed to methods for production of a mutant high alkaline protease; Claims 12-13 and 27 are directed to a method of obtaining an alkalophilic *Bacillus* strain having a reduced extracellular alkaline protease level; Claims 14-15, 29 and 34-35 are directed to an alkalophilic *Bacillus* strain producing a mutant high alkaline protease; Claims 36-37 are directed to a non-reverting alkalophilic *Bacillus* strain comprising a mutated extracellular protease gene; Claim 19 is directed to a detergent composition comprising as an active ingredient a mutant high alkaline protease. Claim 24 is directed to a method of preparing a detergent composition comprising a mutant high alkaline protease as an active ingredient. Claim 25 is directed to a method of processing laundry with the claimed detergent composition. Claims 30-33 are to a method for producing a mutated high alkaline protease free of endogenous extracellular alkaline protease.

The Office Action

Claims 4-7, 9-15, 19, and 23-37 are rejected under 35 U.S.C. 112, first paragraph.

Claim 13, and thus dependent claims 14-15, and claims 26-27, 34, and 35-37 are rejected under 35 U.S.C. § 112, second paragraph.

Claims 19, 24 and 25 are rejected under 35 U.S.C. § 103 as being unpatentable over Fahnestock *et al.* and Estell *et al.*, in view of TeNijenhuis and Suggs *et al.*

Amendments

Claims 11, 15, 26-28, and 36-37 have been cancelled. Claims 4-7, 9-10, 12-14, and 29-35 have been amended. New Claims 38-40 have been added. Claims 12, 23, 29, 30, 33-35 recite that the alkalophilic *Bacillus* strain contains a wild type high alkaline protease gene endogenous to the alkalophilic *Bacillus* strain. This claim would find support, for example on Page 6, lines 17-24, and page 4, lines 18-20. The claims also have been amended to recite that the protease negative strain of alkalophilic Bacilli is a non-reverting strain. The remainder of the changes are to correct clerical and/or typographical errors, and to more clearly set forth that which is claimed. The changes find support in the claims as filed.

No new matter has been added by these amendments and the Examiner is respectfully requested to enter them.

35 U.S.C. § 112, first paragraph.

> Claims 4-7, 9-15, 19, 23-29, 30-37 are rejected under 35 USC § 112, first paragraph, as the disclosure is enabling only for claims limited to methods of producing an alkalophilic asporogenic Bacillus novo species PB92 of minimal natural extracellular protease level, transformed with a B. novo PB92-alkaline-protease which has been mutated as described in the specification. Claims 30-33 are included for the same reasons as the previously rejected claims. See M.P.E.P. 706.03(n) and 706.03(z).
>
> The claims are not properly enabled for the recitation of any "mutant high alkaline protease", and any "alkalophilic Bacillus strain". Applicants have again stated that the strain PB92 has been used merely as an example, and that the specification provides enablement for the use of other types of these strains, and for other "mutant high alkaline proteases". Applicants further state that techniques for such are "routine and require no inventive skill or undue experimentation" (quoted from pg. 7, response of 9-7-93). Finally, applicants have stated that "it is not relevant which asporogenic and/or alkalophilic Bacillus strain is sued to practice the method" (pg. 8 of the 4-17-96 response).
>
> This is not deemed persuasive for the reasons of record. Applicants have not specifically addressed and traversed any apparent deficiencies in the rejection at hand, and within the reasons of record, and thus the rejection is maintained. Again and importantly, there is no teaching or reasonable expectation provided that one skilled in the art would be able to utilize the teachings provided for any other systems/genes, or even that there is a problem with any other source such as that the instant invention would be applicable. Absent this knowledge, one skilled in the art is left with an undue amount of experimentation, due to the breadth of the claims, in order to attempt to determine what other Bacilli or proteases would be useful in the instant invention, and then further attempt to find the gene and apply the principles taught herein. The specification has not provided pertinent information regarding any other "high alkaline protease" gene, nor any appropriate Bacillus strain that would satisfy the requirements of the invention. This fact is important, as the claims are not commensurate in scope with the specification and its enablement. This information is essential to the function of the claimed invention, and the essential material may not be improperly incorporated into the specification, and does not find support within the teachings of the specification. Thus, one skilled in the art would in no way be enabled to practice the claimed invention with any such gene or strain other than the enabled Bacillus PB92.

> Applicants have attempted to add support to the argument by incorporating the statement at page 12 of the specification regarding B. lentus. The Examiner does not see how this statement within the specification provides one skilled in the art with enablement to make and/or use the invention with such a strain. This passage does not appear to connect and directly dictate the use of this strain in the instant method, nor does it provide a reasonable expectation of success, predictability or guidance to use this stain. Even if this were true, the amount of experimentation for one skilled in the art to test this strain, given the parameters discussed in the paragraph above, would be undue, and would not provide enablement for the breadth of the instant claims.

Applicants respectfully draw the Examiner's attention to the fact that M.P.E.P §§ 706.03(n) and 706.03(z) have been deleted from the sixth edition of the M.P.E.P. Applicants also note that the Examiner has not provided grounds of rejection for Claims 34-37 under 35 USC § 112, first paragraph. In any event, Applicants respectfully traverse the Examiner's rejection because the Applicants have provided working examples demonstrating that their claims are enabled, while the Examiner has failed to meet his burden in showing lack of enablement for the pending claims.

The Court of Customs and Patent Appeals addressed the issue of rejection of claims as lacking enablement for being overly broad in *In re Marzocchi*, 439 F.2d 220, 169 USPQ 367 (CCPA 1971). In reversing the Patent Office Board of Appeals decision upholding the claim rejections under 35 U.S.C. § 112, first paragraph, the court stated:

> Turning specifically to the objections noted by the board as indicated above, it appears that these comments indicate nothing more than a concern over the *breadth* of the disputed term. If we are correct, then the relevance of this concern escapes us. It has never been contended that appellants, when they included the disputed term in their specification, intended only to indicate a single compound. Accepting, therefore, that the term is a generic one, its recitation must be taken as an assertion by appellants that all of the "considerable number of compounds" which are included within the generic term would, as a class, be operative to produce the asserted enhancement of adhesion characteristics. The only relevant concern of the Patent Office under these circumstances should be over the *truth* of any such assertion. The first paragraph of § 112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt does exist, a rejection for failure to teach how to make and/or use will be proper on that basis; such a rejection can be overcome by suitable proofs indicating that the teaching contained in the specification is truly enabling. (169 USPQ 369, emphasis therein).

Applicants have demonstrated the truth of the statements within their specification and claims by showing that deletion of the coding region for an endogenous extracellular high alkaline protease in alkalophilic *Bacilli* leads to new and useful strains and methods for production of proteins in alkalophilic *Bacilli* as well as new and useful mutated high alkaline proteases which do not contain wild-type protease endogenous to the host strain in which they are produced. Such strains were shown not to produce endogenous extracellular protease, and to produce high levels of protein from an introduced gene. Applicants are not claiming all Bacilli, but rather a subset of Bacilli generally referred to as alkalophilic Bacilli which are defined as *Bacillus* strains that grow under alkaline conditions (see specification, page 10, lines 21-32). Applicants also are not claiming all proteins, they are not claiming all proteases, but instead have limited their claims to mutated high alkaline proteases derived from alaklophilic Bacilli (see specification page 10, lines 11-14). The working examples provided within Applicants' application demonstrate that the invention as claimed is fully enabled.

The Examiner has not provided a single example of an alkalophilic *Bacillus* or a mutated high alkaline protease which would not function in any of the claimed inventions. Nor has the Examiner provided any sufficient reason to doubt the objective truth of the statements within Applicants' specification. The Examiner has merely repeatedly asserted that the Claims are not properly enabled as one of ordinary skill would not be able to perform the invention with each high alkaline protease from each type of alkalophilic *Bacillus*. The Examiner's rejections therefore are deficient, as the Examiner has failed to meet his burden in showing that the claims are not enabled. Absent any such nonfunctioning examples provided by the Examiner, and in light of Applicants' proof of enablement by their examples, the claims *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 (*In re Marzocchi*, 169 USPQ 367, 369).

A case which involves the issue of support for generically claimed proteins and generically claimed bacteria expressing them is *In re Vaeck*, 947 F.2d 448, 20 USPQ2d 1438. In *Vaeck*, the applicants claimed a chimeric gene "coding for an insecticidally active protein produced by a Bacillus strain, or coding for an insecticidally active truncated form of the above protein or coding for a protein having substantial sequence homology to the active protein ...." Additionally, applicants pursued claims drawn to vectors, insecticidal

compositions, a strain, and to any cyanobacterium expressing such a chimeric gene. In upholding the rejections of claims 1-46 and 50-51 under 35 U.S.C. § 112 first paragraph, the Court of Appeals, Federal Circuit, found the applicants' claims involving all cyanobacteria overly broad where the applicants had only employed one species of cyanobacteria and only disclosed in their specification nine of the more than 150 known genera of cyanobacteria. But the court explicitly stated that "In so doing we do not imply that patent applicants in art areas currently denominated as "unpredictable" must never be allowed generic claims encompassing more than the particular species disclosed in their specification. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." (20 USPQ2d 1445).

The CAFC then reversed the 35 U.S.C. § 112 first paragraph rejections of claims 47 and 48. Claim 47 required that the cyanobacterium be selected from the two disclosed genera *Anacystis* and *Synechocystis*, with its dependent claim 48 limiting the cyanobacterium to *Synechocystis* 6803. The CAFC further noted that "Although these claims are not limited to expression of genes encoding particular *Bacillus* proteins, we note what appears to be an extensive understanding in the prior art of the numerous *Bacillus* proteins having toxicity to various insects." (20 USPQ2d 1445).

In the present case, Applicants' claims involve alkalophilic *Bacilli* and mutated high alkaline proteases. The limitation in Applicant's claims to alkalophilic *Bacilli* is analogous to the two genera found enabled in Vaeck by working exemplification using a single species of cyanobacteria. The limitation in Applicants' claims to mutated high alkaline proteases is narrower than claim 47 of *Vaeck*, which recites genes for any *Bacillus* proteins for which the specification was deemed to have met the requirements of 35 U.S.C. § 112, first paragraph. It would not require undue experimentation for one of skill in the art to practice the invention as claimed. The Examiner's rejection of the currently pending claims under 35 U.S.C. § 112, first paragraph, therefore is improper. The scope of Applicants' claims is consistent with the scope of their disclosure and the scope of their enablement. Accordingly, the Examiner is requested to withdraw the rejection.

> Again, the specification is not properly enabled for claims to any "derivative thereof" of a Bacillus novo species PB92. Applicants state that passages on page 12 of the specification refer to known "derivatives", and that this would be enabling for the instant invention. The phrase "derivatives thereof", however, encompasses predetermined and random mutants of the strain, and progeny of the strain that may or may not contain the gene for the "mutant high alkaline protease" and/or a revertant strain with the indigenous gene. The specification does not properly teach nor describe to one skilled in the art these "derivatives", what specifically they entail, nor is a matter of essential material, without an instant and specific teaching as to how these would be applicable, is not sufficient.

Thus, this results in undue experimentation for one skilled in the art to attempt to produce such without proper guidance from the specification. Applicants have amended claims 4 and 13 to avoid this language, however, it remains for claim 31.

This rejection has been avoided by amendment of Claim 30 from which Claim 31 depends to recite that the host strain is a non-reverting strain which produces no detectable wild type extracellular high alkaline protease endogenous to the host strain. When a derivative of PB92 is the host strain, by definition it has these same characteristics.

While claim 29 was rejected as not properly enabled by the teachings of the specification for the host strain to be "substantially incapable of reversion", new claim 30 was not. This was an oversight on the part of the Examiner. Applicants, however, are encouraged to use these rejections as guidance for the language and enablement of all the claims, and not to assume that the Examiner has performed an exhaustive list of all occurrences (although all such attempts will be made). Applicants appear to have attempted this per the 112 2nd paragraph rejection, in stating that the claims have been amended to delete the word "substantially", however, this occurrence in claim 30 has been overlooked. Claim 30 is rejected for the same reasons of record.

Claim 30 has been amended to remove the word "substantially", and to recite that the strain is non-reverting.

It should again be noted that applicants have pointed out, at page 11 of the response filed 4-17-96, that the Examiner has erred in rejecting claim number 9 under 35 USC 112, 1st paragraph. This is not deemed persuasive. Again, although the claim is specific for one aspect (the gene), but not all, including the strain, and is still properly rejected. This is consistent with the rejections maintained above for both the strain and gene.

This rejection is traversed because as set forth above, Applicants have properly enabled the scope of their claims. The burden is on the Examiner to provide examples of claimed strains which will not work, or reasons to doubt the objective truth of Applicants' statements. The Examiner has done neither. Further, Applicants assert that their working examples overcome any such reasons, and demonstrate that their statements are true. Therefore, the Examiner is respectfully requested to withdraw the rejection.

Claims 26 and 28 are rejected and not enabled for the use of the term "reduced endogenous extracellular protease levels", for the reasons of the rejection set forth with regard to this language in claim 12, etc., as stated at page 3 of the Office Action of 7-15-92 (paper #11). This rejection is in response to applicants amendment, which is an attempt to avoid the new matter rejection of the term "minimal". The phrase "reduced ... levels" has previously been rejected, and applicants have amended other claims to overcome this by the recitation of "no endogenous ... levels".

This rejection has been avoided by cancellation of Claims 26 and 28.

35 U.S.C. § 112, second paragraph.

Claims 13, and thus dependent claims 14-15, and claims 26-27, 34, and 35-37 are rejected under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 13 is rejected as being indefinite as it depends from claim 12. Claim 13 is amended to recite that the strain "contains a mutant high alkaline protease", while the independent claim 12 is not drawn to a method of producing this protease, and does not contain any information as to how this mutant protease is to exist within the strain.

This rejection is believed avoided by amendment of Claims 12 and 13.

Claim 35 is indefinite for the recitation of lines 2-3, in the deletion of "protease", as opposed to the intended protease gene.

Claims 35 and 37 are confusing and apparently redundant, as they recite the prevention of reversion within the strains of claims 34 and 36, but these claims already state that the strains are "non-reverting".

Claim 36 is indefinite for the recitation of the term "endogenous" in the second line, while reciting "exogenous" in the last line. It is unclear as to which one is correct and intended, but as currently recited, conflict.

This rejection is believed avoided by cancellation of Claims 36-37 and amendment of Claim 35 to recite the term "gene".

Claim 26 is indefinite and conflicting, as the preamble states that the protease produced is "free of endogenous extracellular protease", but the next line states that the strain only has "reduced levels" of such proteases.

Claim 26 has been cancelled.

Claim 27 appears to be a substantial duplicate of claim 12. Claim 27 differs from claim 12 only in that in line 5, it does not state "and encoding a replication function". Yet claim 27 requires a replication function in the latter part of the claim, to be inactivated. Thus, the claims do not appear to differ. Also, claim 27 is indefinite as the claim refers to "the replication function" and "said replication function", but these terms lack an antecedent basis within the claim.

Claim 27 has been cancelled.

Claim 34 is indefinite and incorrect for the recitation of "a non-reverting extracellular protease-negative phenotype", as this is only true of the high-alkaline protease phenotype. Elimination of this gene may/would not necessarily result in a strain being completely free of all extracellular proteases. Further, it is confusing as to the necessity or intent of the phrase "an increased efficiency in production of said mutant high alkaline protease as compared to an untransformed strain of the same species". If the untransformed strain never (a) produced the mutant protease, or (b) never produced a high alkaline protease, then it follows that it would naturally have an "increased efficiency in production" of the previously non-existing gene.

This rejection is believed avoided by amendment of Claim 34 to recite that the protease is a high alkaline protease.

35 U.S.C. § 103

Claims 19 and 24-25 remain rejected under 35 U.S.C. § 103 as being unpatentable over Fahnestock et al. and Estell et al., in view of TeNijenhuis and Suggs et al. The references and rejection are herein incorporated as cited in a previous Office Action.

The detergent composition and method preparing such and method for processing laundry utilize "a mutant form of high alkaline protease prepared according to the method of Claim 23". While the remaining claims, directed to methods and strains for producing such proteases are free of the prior art, they do not appear to impart a patentable difference to the protease itself, and thus any detergent composition or method of using or making, each employing the protease determined to have been obvious from the prior art teachings, would also have been obvious. Again, TeNijenhuis describes the natural protease, and various naturally-occurring mutations would have been expected to occur. Further, the recombinant production and mutation in light of the teachings of the instant references would have made the instant composition and methods obvious, absent any clear and convincing evidence to the contrary.

Applicants have received patents (5,336,611 and 5,324,653) directed to specific novel and unobvious mutations of the protease, genes, etc. The instant proteases are not directed nor limited to such mutations.

The rejection of Claims 19, 24 and 25 is respectfully traversed because the cited references, when taken as a whole, would not have made obvious the invention of Claims 19, 24 and 25 at the time the invention was made. The presently claimed invention requires that a mutant high-alkaline protease be produced by the nonobvious process of expression in a nonobvious non-reverting high-alkaline protease negative alkalophilic *Bacillus*; then a detergent composition must be added, and laundry processed using the composition. There is no suggestion of the desirability of mutant high-alkaline proteases free of endogenous high alkaline proteases in the references. There is no suggestion of expression of the gene for mutant high-alkaline proteases in the references, particularly as not even the amino acid sequence, much less the gene itself, was known. There is no suggestion in the references to delete the gene for the high-alkaline protease to generate a non-reverting high-alkaline protease-negative phenotype; on the contrary, there is a suggestion that this deletion might be lethal. There is no suggestion in the cited references that alkalophilic *Bacilli* would make useful host cells. There is no suggestion in the references to add a detergent composition to mutant high-alkaline proteases, and finally, there is no suggestion in the references to process laundry with the resulting composition.

Claims to methods of producing a non-reverting high-alkaline protease deficient strains, the strains themselves, and the methods of producing mutant proteases in such strains are deemed free of the prior art (Paper 41, page 8, mailed September 4, 1996). However, the Examiner has cited the same references which have been overcome for these claims in rejecting the method of preparing a detergent composition from a novel and non-obvious mutant high-alkaline protease produced by a novel and non-obvious method, the resulting detergent composition containing the novel and non-obvious mutant high-alkaline protease, and a method for processing laundry using the detergent composition containing the novel and non-obvious method.

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success.

Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Cited References Do Not Teach All the Claim Limitations

The Examiner has provided neither citations nor sound scientific reasoning to satisfy even one of the three prongs of the prima facie case of obviousness. There was no motivation or suggestion to combine the references as he has done. There was no reasonable expectation of success in achieving the present invention even if the cited references are combined and modified as the Examiner would suggest. Finally, even should the references be combined and modified as the Examiner would do, one would not achieve all the claim limitations of the present invention.

Here, the references have already been found insufficient to render the methods of producing mutant high-alkaline proteases in the non-reverting protease deficient strains obvious. The method of producing a detergent composition comprises the additional step of adding a detergent composition to the mutant protease thus produced. The method of processing laundry comprises the additional step of adding the resulting composition to laundry. Adding additional steps to an already nonobvious process can only result in further nonobvious processes. The cited references teach nothing further in the area of detergent compositions containing mutant high-alkaline proteases than they do in the nonobvious area of producing such mutant proteins. The Examiner has combined and modified the references in a way that no person of ordinary skill in the art would have done at the time the instant invention was made.

For the foregoing reasons, Applicants assert that the cited references do not render the invention of Claims 19, 24 and 25 obvious. Accordingly, the Examiner is respectfully requested to withdraw the rejection under 35 U.S.C. § 103.

## CONCLUSION

In view of the above amendment and remarks, it is submitted that this application is now ready for allowance. Early notice to that effect is solicited. If in the opinion of the

Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is invited to call the undersigned attorney at (415) 328-4400.

Respectfully submitted,

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